REMARKS

Claims 1, 4-35 and 38-63 are pending. Claims 1, 35, 62 and 63 are proposed to be amended herein. Claims 25-27 and 53-55 are cancelled herein. The amendments add no new matter.

New claims 64-67 are proposed to be added herein. Claims 64-67 correspond to claims 1, 35, 62 and 63 as originally filed and examined, with the additional limitation in each requiring "wherein said separating comprises capillary electrophoresis," which limitation was considered with regard to the original claims in, for example, original dependent claims 26 and 54. New claims 64-67, in contrast to claims 1, 35, 62 and 63 as presently pending, lack the limitations reciting "at least five" templates/transcripts in the respective methods. The new claims also recite PCR amplification, which has been previously considered during examination in the context of, for example, dependent claim 16.

The limitations regarding "at least five" templates/transcripts were not accepted by the Examiner as providing patentable distinction over the art. In view of the Declaration and arguments over the Wiesner reference presented herein (see below), Applicant believes that the "at least five" limitations are not necessary to distinguish the art. The entry and consideration of claims 64-67, particularly in view of the Declaration and arguments over the Wiesner reference presented herein, is respectfully requested.

Rejections under 35 U.S.C. §103:

Claims 1, 4-35 and 38-63 are rejected as obvious under 35 U.S.C. §103(a) over Wiesner (Nucleic Acids Res. 1992) in view of Schumm et al. (U.S. 6,479,235).

Claims 35 and 38-61 are also rejected as obvious under 35 U.S.C. §103(a) over Wiesner in view of Brenner (U.S. 6,228,589), and further in view of Schumm et al. The Office Action states the following with respect to the Wiesner and Schumm et al. references:

> Wiesner teaches methods of quantitatively amplifying a plurality of nucleic acids, wherein an aliquot of the amplification mixture is dispensed or withdrawn at plural stages during the amplification regiment; see entire document on pages 5863-5864.

Wiesner does not disclose use of at least five different amplification templates, nor the use of capillary electrophoresis for nucleic acid separation.

Schumm et al. disclose the well-known technique of multiplex amplification wherein a plurality of different nucleic acid targets (at least thirteen; see abstract) are simultaneously amplified, and that electrophoresis, preferably capillary electrophoresis, is used to separate the different products produced in multiplex amplification (see column 14, lines 52-64).

One of ordinary skill in the art would have been motivated to use a plurality of amplification targets, such as at least five, as well as the technique of capillary electrophoresis, in the method of Wiesner, because the advantages of both multiplex amplification and capillary electrophoresis were well known and common knowledge in the art, as demonstrated by Schumm et al. In other words, the skilled artisan considering these references would have been motivated to apply multiplex amplification and capillary electrophoresis as taught by Schumm et al. in the method of Wiesner to provide the obvious advantage of facilitating quantitative amplification profiles of large numbers of target nucleic acids. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods.

With respect to Wiesner, Brenner and Schumm et al., as applied to claims 35 and 38-61, the Office Action states:

These claims are drawn to methods similar to those discussed and rejected above, wherein two amplification reactions corresponding to two gene expressing entities are carried out, and the resulting expression or transcription profiles are compared.

The teachings of Wiesner and Schumm et al. are discussed above.

Neither of these references teaches comparison of gene expression or transcription profiles from two different gene expressing entities.

Brenner discloses methods of measurement of gene expression profiles for use in toxicity screening, comprising comparing gene expression profiles from two different gene expressing entities (test vs. control organisms) (see column 5, line 66 to column 6, line 20).

One of ordinary skill in the art would have been motivated to carry out the method of Wiesner using two different gene expressing entities and comparing the resulting expression profiles, because as taught by Brenner such a comparison of gene expression profiles provides valuable information on the different states of the two entities, for example regarding toxicity after drug exposure. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods.

The Office Action continues:

Wiesner is cited <u>not</u> for the particulars of the multiplex amplification reaction, but for the teaching of <u>quantitatively</u> amplifying a plurality of nucleic acids,

> wherein an aliquot of the amplification mixture is dispensed or withdrawn at plural stages during the amplification regimen. Schumm et al. disclose that the skilled artisan was well aware of the multiplex amplification conditions required to amplify at least thirteen amplification templates. There would have been both suggestion and reasonable likelihood of success for combining these teachings to achieve the expected benefits of the quantitative results of Wiesner and the multiplex reactions of Schumm et al. having at least thirteen templates. Thus the rejections are maintained. (Emphases in original)

Applicant respectfully disagrees.

First, Applicant proposes herein to amend each of the independent claims (i.e., claims 1, 35, 62 and 63) to recite "wherein said separating comprises capillary electrophoresis." This limitation was recited in original claims 26 and 54 and therefore neither adds new matter nor raises new issues for examination. Entry of the amendment is respectfully requested.

Next, Applicant submits that the teachings of Wiesner, which teaches the use of slab gel electrophoresis in a specific assay to provide quantitative information, are not applicable or adaptable to a capillary electrophoresis format. As described in the accompanying Declaration of inventor Dr. Vladimir Slepnev under Rule 132, the quantitative method of Wiesner requires knowledge of both: (a) the actual volume of PCR reaction sample applied to the electrophoretic separation; and (b) precise measurement of the absolute amount of amplified PCR product contained within a separated peak. That is, Wiesner describes a method in which quantitative information regarding the amount of initial template in a PCR reaction can only be determined if these two parameters are known. As discussed by Dr. Slepnev in the Declaration, unlike the slab gel electrophoresis method taught by Wiesner, neither of these parameters are satisfied or known when capillary electrophoresis is used to separate and detect nucleic acids as recited in the claims as proposed to be amended herein.

In section 5(A) of the declaration, Dr. Slepnev explains that Wiesner's "method is based on the exact knowledge of the volume of the aliquot subjected to separation, which becomes the basis for all calculations." Dr. Slepnev explains that "[w]hereas the entire volume of the aliquot placed into the slab gel goes into the separation, only a small and unknown portion of the aliquot placed for injection into the capillary actually enters the capillary" during capillary electrophoresis.

In section 5(B) of the declaration, Dr. Slepnev explains the difficulties involved in measuring the absolute amount of amplified PCR product contained within a separated peak as is also required for quantitation according to Wiesner's method. Dr. Slepnev details the difficulties involved in radioactive detection in CE, UV detection in CE, and absolute quantitation by fluorescence in CE.

The Final Office Action emphasizes that "Wiesner is cited not for the particulars of the multiplex amplification reaction, but for the teaching of quantitatively amplifying a plurality of nucleic acids, wherein an aliquot of the amplification mixture is dispensed or withdrawn at plural stages during the amplification regimen" (emphases in the original). However, as detailed by Dr. Slepnev in the accompanying declaration, in order to achieve the quantitation that is central to Wiesner's method, one must know both the actual volume of sample applied to the separation and the absolute amount of amplified PCR product in a separated peak. Values for these parameters are required in order to solve for the quantitative information on initial target nucleic acid amount, and because these values are not known for capillary electrophoresis, one of skill in the art cannot use capillary electrophoresis in the quantitative method described by Wiesner. This conclusion is supported by Dr. Slepnev's Declaration, in which he concludes that "quantitation as taught by Wiesner cannot be achieved using capillary electrophoresis" and that "the method of Wiesner requires specific means described in the reference and that capillary electrophoresis cannot be simply substituted for slab gel electrophoresis if one expects to use the template nucleic acid quantitation approach that is central to the teachings of the Wiesner reference." Because Wiesner's method cannot be adapted to capillary electrophoresis and still maintain the quantitative aspect which is both central to Wiesner's teachings AND acknowledged by the Office Action to be central to the present rejection, Applicant submits that no combination of the teachings of Wiesner with the capillary electrophoresis-related teachings of Schumm et al. can render obvious the invention as presently claimed. This defect is not remedied by the addition of any teachings of the Brenner reference.

In view of the above, Applicant submits that none of the claims as proposed to be amended can be obvious over the proposed combinations of Wiesner, Schumm et al. and Brenner. Reconsideration and withdrawal of the §103(a) rejections over these references is respectfully requested.

In view of the above, all issues raised in the Final Office Action have been addressed herein. Entry of the proposed amendments and claims and reconsideration of the claims is respectfully requested.

Respectfully submitted:

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Mark J. FitzGerald
Reg. No. 45,928
Attorney for Applicant
NIXON PEABODY LLP
100 Summer Street
Boston, MA 02110-2131
(617) 345-1058 (Ph)
(617) 345-1300 (Fax)